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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,568	10/23/2003	Hirohiko Tsuzuki	Q77913	5986

23373 7590 08/11/2005

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EXAMINER	
SINGH, SATYENDRA K	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/690,568	TSUZUKI ET AL.	
	Examiner	Art Unit	
	Satyendra K. Singh	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *11-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

Applicant's response (dated the June 15th, 2005) to the election requirement and election without traverse, of group I, claims 1-10 for examination is acknowledged.

Claims 1-10 are examined on their merits, hereafter.

Abstract

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because it contains improper language '**such as**" and "**and the like**" in first and second line on page 27 of the instant specification. The appropriate correction is required. See MPEP § 608.01(b).

Claim Objections

Claim 9 is objected to because of the following informalities:

Claim 9 recites "the method according to **any one of claims 1**". Since the instant specification has only one claim 1, for examination purposes (*in lieu* of the claimed subject matter) it is assumed that claim 9 is drawn to "a method according to any one of the compounds according to claim 1". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "A method for detaching a carrier for cell culture from a cultured cell formed on a surface of said carrier for cell culture, which comprises the step of bringing the carrier for cell culture into contact with a compound represented by the following formula (I):

MO_3P----L11----PO_3M

Wherein L11 represents a divalent bridging group; and M represents hydrogen atom or a cation, or a polyphosphoric acid or a salt thereof".

The claimed invention is confusing because of the use of semi-colon after the term "bridging group" and a comma after the term "cation". It is not clear whether the limitations after the semi colon are part of the formula (I), and if they are part of the formula (I), whether all the limitations after the semi colon are represented by the symbol M? Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hara et al (U.S. Patent 6,821,107 B1, [A]) in view of Brenden et al (U.S. Patent 5,292,525, [B]).

Claim 1 is drawn "to a **method for detaching a carrier** for cell culture from a cultured cell formed on a surface of said carrier for cell culture, which comprises the step of bringing the carrier for cell culture into **contact with a compound** represented by the following **formula (I)**: (as claimed in the instant specification-see page 24) wherein L11 represents a divalent bridging group; and M represents hydrogen atom or a cation, or **a polyphosphoric acid** or **a salt thereof**".

As evidenced by claims 2-4, it appears that applicant's claim 1 is drawn to "a method for detaching a carrier for cell culture from a cultured cell formed on a surface of said carrier for cell culture, which comprises the step of bringing the carrier for cell culture into contact with a compound represented by the following formula (I): (as claimed in the instant specification-see page 24) wherein L11 represents a divalent bridging group and M represents hydrogen atom or a cation, or a polyphosphoric acid or a salt thereof".

Claim 2-6 drawn to variations of the method of claim 1. Claim 2 is drawn to a methods for culturing a cell; claim 3 is drawn to a method for transferring a cell; claim 4 is drawn to a method for laminating cell layers; claim 5 is drawn to a method wherein the carrier for cell culture comprises a calcium alginate gel layer; and claim 6 is drawn to a method wherein the carrier for cell culture comprises laminated calcium alginate gel layer and cell adhesion gel layer.

Hara et al [A] teach a method for formation of multiple cell layers on a carrier for cell culture having an alginate gel layer (with or without extracellular matrix component, such as collagen) formed on a porous membrane (see prior art, abstract, Fig. 1, 2, and 3, and summary of the invention, in particular), wherein a method for detaching a carrier for cell culture from a cultured cell formed on a surface of said carrier for cell culture comprises the step of bringing the carrier for cell culture into contact with a compound such as a chelating agent (ethylenediaminetetraacetic acid, EDTA) in order to solubilize and detach the cultured cell layer from the carrier from cell culture (porous membrane) (see prior art, columns 2-6, and examples 1-3, in particular) for lamination purposes.

Prior art [A] teaches the fact that the chelating compound used for solubilizing and detaching the carrier for cell culture (from cultured cells formed on alginate-based carrier) can be selected appropriately (from polyaminocarboxylic acids and oxycarboxylic acids) according to the type of a multivalent metal ion which forms a chelate structure with a carboxylic acid group in the molecule of alginic acid (see prior art, column 6, third paragraph, in particular).

Hara et al [A] teach the method for culturing a cell by using a carrier for cell culture (such as sodium alginate gel layer with collagen layer made on a porous membrane) comprising the steps of bringing a cell culture containing a cultured cell (fibroblast cell layer) adhered on a surface of the carrier for cell culture into contact with a chelating agent such as EDTA, and detaching the cultured cell from the cell culture and transplanting said cell on a surface of other cultured cell (see Figs. 2-3; column 3-6; example 2; and example 3, steps 1 and 3, in particular).

Hara et al [A] teach the method for transferring a cell, which comprises the steps of culturing a cultured cell (fibroblasts cell layer) formed on a carrier for cell culture (made of sodium alginate, and collagen gel layers, in any combination) while said cultured cell is allowed to be in contact with a surface of other carrier for cell culture with weighting (see column 3-6; figs. 2-3; and examples 2-3, in particular) and bringing a cell culture obtained in the aforementioned step into contact with a chelating agent such as EDTA to detach the carrier for cell culture by dissolving the alginate layer (see examples 2 and 3 for multilayer cell culturing and piling up cell layers, in particular).

Hara et al [A] teach a method for laminating cell layers, which comprises the steps of: culturing a cultured cell (such as fibroblast cells) formed on a carrier for cell culture (such as alginate or alginate with collagen, in any combination thereof) while said cultured cell is allowed to be in contact with other cultured cell with weighting (see column 6, in particular); and bringing a cell culture obtained in the aforementioned step into contact with a chelating agent such as EDTA (see example 3 and steps therein, in particular) to detach the carrier for cell culture.

Hara et al [A] teaches a method such as claimed wherein the carrier for cell culture comprises a calcium alginate gel layer (see Fig. 1; column 3-6; and example 1, in particular); and wherein the carrier for cell culture comprises laminated calcium alginate gel layer and cell adhesion gel layer (referred as "ECM component sponge" made of extracellular matrix material, collagen) (see Figs. 2 and 3; column 3-6; and example 1, in particular).

As discussed individually (supra), Hara et al [A] teach the method of forming a structure having multiple cell layers using carrier for cell culture made of calcium alginate and collagen gel layers on a porous membrane support. Hara et al [A] also teaches laminated carriers for cell culture, method for culturing cells using the carriers, method of transferring cultured cells obtained by the method of culturing cells and detaching them from the carrier for cell culture using a chelating compound such as EDTA, a method of laminating (piling up) another cell layer on the cultured cell layer, and a cell multi-layer obtained by this lamination procedure (see Hara et al [A], entire document).

However, the method step of bringing the carrier for cell culture into contact with a compound represented by formula (I) of claim 1, wherein L11 represents a divalent bridging group and M represents hydrogen atom or a cation, or a polyphosphoric acid or a salt thereof, is not explicitly disclosed.

Brenden et al [B] teach a method and composition for removing an alginate from a cutaneous substrate (such as, alginate wound dressings from human or animal or animal wounds, skin, or cellular tissue), wherein the composition contains at least one chelating agent, the most preferred being the water soluble phosphates such as sodium hexametaphosphate (SHMP or HMPA or Calgon-T, one of the exemplifications used in the instant specification) (see Brenden et al [B], abstract; summary of the invention; and column 5, 3rd and 4rth paragraphs, in particular) used to solubilize/remove alginate containing wound dressings. Brenden et al also teach that in theory, **any chelant (chelating agent) which solubilizes a counter ion found in an alginate** wound dressing can be used which include but are not limited to a) organic acids (including EDTA, etc.); b) **chelating polyphosphates** (such as metaphosphates, pyrophosphates, or polyphosphates); and c) polymers (see prior art [B], column 4, last paragraph; entire column 5 and 6, in particular). Prior art also states the fact that the compositions containing polyphosphates are generally believed to be less toxic than compositions containing either the organic chelating agents (such as EDTA) or the polymeric (such as anionic vinyl addition polymers) sequestrants/chelating agents cited in the prior art (see prior art [B], column 6, first paragraph; tables 1-3, in particular).

Therefore, it would have been obvious to a person of ordinary skill in the art to modify the methods for detaching a carrier for cell culture from a cultured cell formed on a surface of said carrier for cell culture which comprises the step of bringing the carrier for cell culture into contact with a chelating compound (as taught by Hara et al [A]) represented by formula (I) (wherein L11 is a divalent bridging group and M is a hydrogen atom or a cation), or **a polyphosphoric acid or a salt thereof** (such as claimed in claim 1 of the instant application) such that the chelating compound used is a chelating polyphosphoric acid or a salt thereof as taught by the prior arts Brenden et al [B].

The person of ordinary skill in the art would have been motivated to make that modification (i.e. replacement of EDTA or other organic acids as chelating agents with polyphosphoric acid derivatives or salts thereof) because Brenden et al [B] explicitly teach the benefits of (see Brenden et al [B], summary of the invention; column 3, 3rd paragraph; and column 6, first paragraph, in particular) using chelating polyphosphates as they are generally known to be superior to the organic acids (such as EDTA, EGTA, etc.) and polymeric sequestrants (such as anionic vinyl addition polymers) in terms of their **toxicity** (and thus teaches the implicit **biocompatibility of chelating polyphosphates** when in contact with living cells or tissues) to biological systems.

One of the ordinary skill in the art would have had a reasonable expectation of success when modifying the methods for detaching the carrier for cell culture as taught by Hara et al [A] by replacing the chelating agent, EDTA used in the Hara et al with a chelating polyphosphoric acid or a salt thereof (such as hexametaphosphate, HMPA) as

explicitly taught by Brenden et al [B] because the Brenden et al [B] explicitly teach the method (as discussed, supra) of removing alginate from the wound dressings used on cutaneous substrates.

Since the benefits accruing from such a modification would provide an effective, biocompatible, and non-toxic alternative to the use of EDTA (which is explicitly taught by Brenden et al [B], to be toxic to the fibroblast cells in a cell culture based cytotoxicity protocol; see prior art, column 9-12, and table 1-3, in particular) as a chelating agent. One of ordinary skill in the art would have been motivated to make such a substitution in the methods for detaching a carrier for cell culture from cultured cell formed on a surface of said carrier for cell culture as claimed.

Thus, the invention as a whole would have been *prima facie* obvious to one skill in the art at the time the claimed invention was made.

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hara et al (U.S. Patent 6,821,107 B1, [A]) in view of Esser et al [U].

Claim 1 is drawn to a method for detaching a carrier for cell culture from a cultured cell formed on a surface of said carrier for cell culture, which comprises the step of bringing the carrier for cell culture into contact with a compound represented by the following **formula (I)**: (as claimed in the instant specification-see page 24) wherein

L11 represents a divalent bridging group; and M represents hydrogen atom or a cation, or a polyphosphoric acid or a salt thereof.

Claim 2-6 drawn to variations of the method of claim 1. Claim 2 is drawn to a methods for culturing a cell; claim 3 is drawn to a method for transferring a cell; claim 4 is drawn to a method for laminating cell layers; claim 5 is drawn to a method wherein the carrier for cell culture comprises a calcium alginate gel layer; and claim 6 is drawn to a method wherein the carrier for cell culture comprises laminated calcium alginate gel layer and cell adhesion gel layer.

Claims 7-10 however, are drawn to methods of detaching a carrier for cell culture using **a compound represented by the formula (I), or (II), or (III)** with various substitutions at L and R groups as claimed, which are exemplified by compounds, namely 1-hydroxyethane-1,1-diphosphoric acid (HEDP/EHBP) and ethylenediamine-N.N,N',N'-tetrakis(methylenephosphoric acid) (EDTPO/EDTMP) used in the instant invention (see instant specification, page 20-22, in particular).

Hara et al [A] teach a method of forming a structure having multiple cell layers using carrier for cell culture made of calcium alginate and collagen gel layers on a porous membrane support. Hara et al [A] also teaches laminated carriers for cell culture, method for culturing cells using the carriers, method of transferring cultured cells obtained by the method of culturing cells and detaching them from the carrier for cell culture using a chelating compound such as EDTA, a method of laminating (piling up) another cell layer on the cultured cell layer, and a cell multi-layer obtained by this lamination procedure (see Hara et al [A], entire document).

However, the step of bringing the carrier for cell culture into contact with a compound represented by formula (I), formula (II), or formula (III) for the methods such as claimed, is not explicitly disclosed by Hara et al [A].

Esser et al [U], using copper-complexation index, teach the fact that chelating agents include (among others such as EDTA, EGTA, etc.) compounds, namely 1-hydroxyethane-1,1-diphosphoric acid (HEDP/EHBP) and ethylenediamine-N.N,N',N'-tetrakis(methylenephosphoric acid) (EDTPO/EDTMP) that are also exemplified by the instant invention (see instant specification, page 20-22, in particular), and are known to be used as chelating agents in the prior arts (see Esser et al [U], abstract, introduction, results & discussion, pages 250, 251 and 255, in particular).

Since the structural limitations of claims 1-10 using a compound for detaching the cell culture carrier from cultured cell formed on a surface as represented by formulas (I), (II) and (III) are met by the species of compounds such as HEDP and EDTPO/EDTMP that are exemplified by the instant specification (see pages 20-22, in particular), it would have been obvious to a person of ordinary skill in the art at the time this invention was made to modify the method for detaching a carrier for cell culture from a cultured cell formed on a surface of said carrier for cell culture comprising the step of bringing the cells culture carrier into contact with a compound as taught by Hara et al [A] such that a compound used for the method for detaching the carrier such as claimed is represented by the formula (I), (II), and (III) such as HEDP or EDTPO/EDTMP as taught by Esser et al [U].

The person of ordinary skill in the art would have been motivated to modify the method by substituting the chelating agent EDTA used in the referenced method of Hara et al [A] with safer, effective, and biocompatible chelating agents such as organophosphates, HEDP, EDTPO/EDTMP, and/or their derivatives as taught by Esser et al [U] because of their functional equivalence in terms of their chelating properties recognized by art at the time this invention was made.

One of ordinary skill in the art would have had a reasonable expectation of success when updating the method for detaching the carrier for cell culture as taught by Hara et al [A] by the above mentioned organophosphates or polyphosphoric acid or salts thereof such as taught by Esser et al [U], because the chelating properties of such compounds is clearly demonstrated by Esser et al [U].

In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. In re Ruff, 256 F.2d 590, 118 USPQ 340 (CCPA 1958).

An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)- see MPEP 2144-06).

Thus the entire invention as a whole would have been *prima facie* obvious to one skilled in the art at the time the claimed invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyendra K. Singh whose telephone number is 571-272-8790. The examiner can normally be reached on 9-5MF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Satyendra K. Singh

JEAN C. WITZ
PRIMARY EXAMINER